REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, claims 58-63 were pending in this application. With this amendment, claim 63 has been canceled without prejudice, and claim 58 has been amended to correct a minor formal error. Claims 58-62 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

I. Specification

As requested by the PTO, Applicants have reviewed the application and deleted all references to embedded hyperlinks and/or browser-executable code. Further, the ATCC address on page 376, line 34, has been amended and the paragraph beginning at page 378, line 33, has been amended to comply with the provisions of the Budapest Treaty. Applicants would like to indicate that Applicants recently made a photocopy of U.S. Application 09/918,585 filed 7/30/2001, of which the instant application is a continuation, from the PTO's files. Applicants respectfully submit that all references to page and line numbers made throughout this response will be based on the application photocopied from the PTO's files by the Applicants.

II. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 58 and 63 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants believe that the PTO mistakenly refers to claim 58 as claim "59" on page 2 (5 lines from bottom).

The PTO alleges that claim 58 recites an antibody that binds a specific polypeptide and that claim 63 recites an antibody that specifically binds the same polypeptide. The PTO further states that neither the specification nor the art defines the difference between an antibody that "binds" and one that "specifically binds." Accordingly, the PTO alleges that the "metes and bounds of the claims cannot be determined by one skilled in the art."

Applicants respectfully disagree. Applicants submit that the art-recognized meaning of "specifically binds" is that the antibody binds to a particular antigen with specificity and does not significantly cross-react with another antigen. Therefore, the term "specifically binds" in claim 63 clearly refers to the antibody of claim 58 that is able to bind to the polypeptide of SEQ ID NO:132 without significantly cross reacting with another antigen. However, solely to facilitate the prosecution of the present application, claim 63 has been canceled without prejudice. Accordingly, the rejection of claim 63 is believed to be moot, and should be withdrawn.

Further, Applicants submit that the cancellation of claim 63 obviates the need for differentiating between an antibody that "binds" and one that "specifically binds." Because one skilled in the art surely understands the meaning of an antibody that binds a specific polypeptide, Applicants submit that the metes and bounds of claim 58 would easily be determined by one skilled in the art. Accordingly, Applicants request that the rejection of claim 58 under 35 U.S.C. § 112, second paragraph, be withdrawn.

III. Claim Rejections Under 35 USC §§ 101 and 112, First Paragraph (Enablement)

Claims 58-63 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility." Claims 58-63 are further rejected under 35 U.S.C. § 112, first paragraph allegedly because one skilled in the art would not know how to use the claimed invention "since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility."

While the PTO acknowledges, on page 4 of the instant Office Action, that the disclosure that PRO351 tested positive in lung tumor sample in a gene amplification assay establishes utility for the PRO351 gene, the PTO contends that it does not establish a utility for PRO351 polypeptides or antibodies. For the reasons outlined below, Applicants respectfully disagree.

Applicants submit that the cancellation of claim 63 renders the rejection of this claim moot. With respect to claims 58-62, Applicants submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that the antibodies of claims 58-62 possess a credible, specific and substantial asserted utility.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974); *see, also In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the PTO has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

A *prima facie* case of lack of utility has not been established

The PTO bases its conclusion that gene amplification does not reliably correlate with increased mRNA transcript or polypeptide levels, and hence its conclusion that PRO351 polypeptides and antibodies lack utility, on Pennica *et al.*, Konopka *et al.*, and Haynes *et al.*

The PTO cites Pennica *et al.* to suport its argument that gene amplification does not reasonably correlate with increased mRNA or polypeptide levels. According to the PTO, Pennica *et al.* teaches that "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression, ...* In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." (Emphasis added). Applicants submit that the PTO has omitted to disclose that in the same paragraph, Pennica also explains that the reason for the absence of correlation between amplification and over-expression may be because the gene was believed to

be amplified, whereas it really was not — "it is possible that the *apparent* amplification observed for *WISP-2* may be caused by another gene in this amplicon." Emphasis added. Accordingly, Applicants respectfully submit that Pennica teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded polypeptide. Further, Applicants do not claim that the utility of the instant invention is the over-expression of *WISP-2* mRNA.

The PTO also cites the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to amplification of the *abl* gene . . . ." Applicants respectfully submit that Applicants do not claim that the utility of the instant invention is the over-expression of the *abl* gene.

Lastly, the PTO cites Haynes *et al.* to show that there was a "general trend but no strong correlation between protein [expression] and transcript levels" for 80 *yeast* proteins. Haynes *et al.*, adds that "[f]or **some** genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold." (Emphasis added).

Based on the above, the PTO concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist.

The PTO has not shown whether the lack of correlation between gene amplification and polypeptide over-expression observed for WISP-2 polypeptides, or the abl gene, or some genes in a family of 80 yeast genes is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, *a correlation between DNA amplification and over-expression of polypeptide* ***was observed*** *in the case of WISP-1*. Similarly, Haynes *et al.*, state that **some** genes **did** show a correlation between increased mRNA levels and translated protein.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Assuming *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Applicants submit is not true,

a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO351 polypeptide and for antibodies that bind to PRO351, for example, in detecting over-expression or absence of expression of PRO351. Further, based on this utility and the

disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed antibodies.

In view of the above, Applicants request the PTO to reconsider and withdraw the rejection of claims 58-62 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below. Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C11**).

Respectfully submitted,

Date: April 29, 2004

By: _____
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